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Gene Section
Review

ING3 (inhibitor of growth family, member 3)

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Abstract

Review on ING3, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: Eaf4, ING2, MEAF4, p47ING3

HGNC (Hugo): ING3

Location: 7q31.31

DNA/RNA

Description

In 1996, Karl Riabowol's group identified a new Tumor Suppressor Gene (TSG) by using subtractive hybridization between cDNAs from normal mammary epithelial cells and mammary epithelial cells from tumor. This experiment was followed by an in vivo screen for tumourigenesis. Using this method, the authors identified a new candidate TSG that they named ING1 for INhibitor of Growth 1 (Garkavtsev et al., 1996). Few years later, ING2, ING3, ING4 and ING5 were identified by homology search. ING3 was identified through bioinformatic analyses in order to find human EST clone showing a high homology with the p33ING1b and p33ING2 cDNAs (Nagashima et al., 2003).

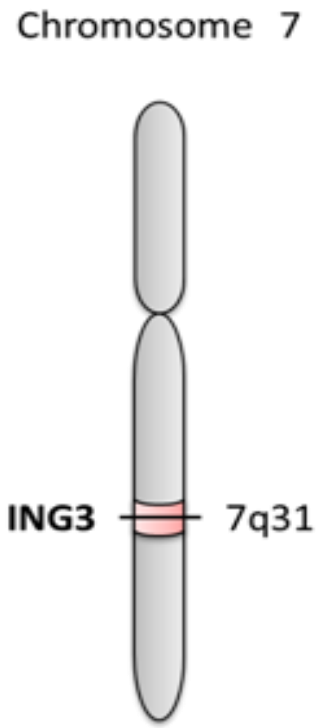

Figure 1. Chromosomal localization of the ING3 gene in Homo sapiens.

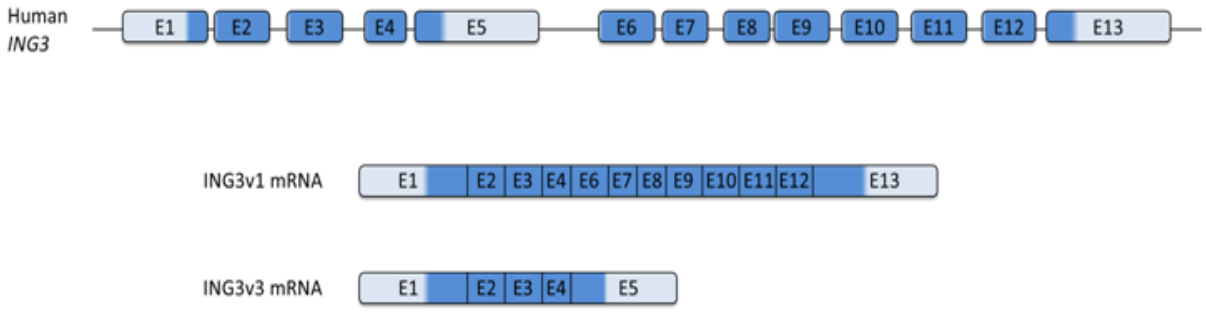

Figure 2. Structure and transcripts of Human ING3 genes. Coding regions are in dark blue and non-coding regions are represented in light blue.

Transcription

The ING3 gene has been mapped to chromosome 7 at locus 7q31. Interestingly, unlike ING1, 2, 4 and 5, ING3 is located far from telomeric regions and is evolutionarily distinct from the other (Fig.1) (He et al., 2005). Human ING3 is made of twelve exons, resulting in 2 transcribed variants (ING3v1a, ING3v3) (Fig.2).

Pseudogene

INGX is the pseudogene of ING (He et al., 2005).

Protein

Description

The ING proteins are characterized by the presence of a highly conserved PHD in their C-terminal part. This domain is commonly found in proteins involved in chromatin modification (Bienz, 2006; Mellor, 2006). The C-terminal part of ING3 isoform contains a Leucine Zipper-Like domain (LZL) and a Novel Conserved Region (NCR) (Fig.3).

Expression

ING3 is ubiquitously expressed in mammalian tissues. Moreover, ING3 expression is increased in oocytes from Human, Rhesus monkey and mice (Awe and Byrne, 2013).

Localisation

ING3 contains an NLS domain, so it is mainly located in the nucleus.

Function

ING3 is a candidate tumor suppressor gene. ING3 regulates apoptosis in a p53 dependent and independent manner.
Indeed, ING3 activates bax transcription through p53 and promotes apoptosis via Fas/caspase 8 pathway in melanoma cells (Nagashima et al., 2003; Wang and Li, 2006).
Moreover, ING3 is a member of the human NuA4 histone acetyltransferase (HAT) complex which is involved in transcriptional activation of genes through acetylation of histones H4 and H2A (Doyon et al., 2004).
ING3 through its involvement in the NuA4 HAT complex regulates the expression of mTOR. Consequently, ING3 regulates oocyte polarization and asymmetric division during oocyte mice maturation through the mTOR pathway (Suzuki et al., 2013).

Implicated in

Ameloblastoma

The analysis of LOH (loss of heterozygosity) for ING genes family, in 33 samples of ameloblastoma cases, showed a high percentage of allelic loss (48.5%) for ING3 gene.
Moreover, there is a strong correlation between the inactivation of ING3 gene and tumor aggressiveness (Borkosky et al., 2010).

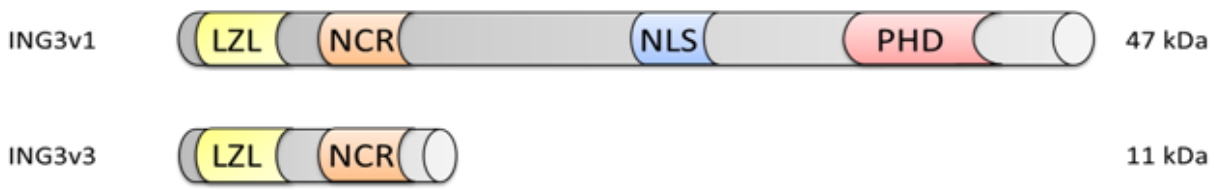

Figure 3. Schematic representation of ING3 proteins structure. In the C-terminal part: Nuclear Localization Signal (NLS), Plant Homeo Domain (PHD). In the N-terminal part: Leucine Zipper-Like domain (LZL), Novel Conserved Region (NCR).

Breast cancer

The analysis of ING3 status in 9 breast cancer cell lines revealed a downregulation of ING3v1 and v3 mRNA in 2 of these cell lines. However, their mRNA abundances were increased in seven other cell lines compared to normal breast epithelial cells (Walzak et al., 2008).

Colorectal carcinoma

In colorectal carcinoma, the ING3 mRNA expression was reduced compared to colorectal non-neoplastic mucosa (NNM). In addition, the expression of ING3 protein has been detected in the cytoplasm but not in the nucleus. Moreover, there is no difference of ING3 protein level between NNM and carcinomas tissues. However, the expression of ING3 was not correlated to the prognosis of patients with colorectal cancer. These results suggest that downregulation of ING3 may have a significant role in colorectal carcinogenesis (Gou et al., 2014).

Cutaneous melanoma

In malignant melanoma, nuclear expression of ING3 was reduced compared to dysplastic nevi, while an increase of cytoplasmic expression is found, in 24%, 39%, and 62% of the dysplastic nevi, primary melanoma, and metastases, respectively. In addition, the location of primary melanomas and the upregulated ING3 cytoplasmic expression are not correlated. In patients with strong nuclear ING3 staining, the survival rate reached 93%, whereas in patients with negative-to-moderate nuclear ING3 staining, the survival rate was just 44%. These findings suggest that ING3 is an important factor for melanoma prognosis and progression (Wang et al., 2007).

Head and neck squamous carcinoma

The analysis of loss of heterozygosity in 49 head and neck squamous cell carcinoma (HNSCC) showed that 48% had an allelic deletion detected in 2 regions on chromosome 7q31 where ING3 is mapped. In addition, only one sample showed a missense mutation manifested by nucleotide change from GAC to GGC at codon 20 which leads to an amino acid substitution from aspartic acid to glycine. A silent mutation from GAC to GAT has been detected in three samples at codon 356 with no amino acid change. Moreover, 50% of primary tumor tissues and 75% of tumor derived cell lines showed a decreased expression of ING3 mRNA. In one case, a complete loss of ING3 mRNA has been detected in 2 primary tissues. In this study, a significant decrease of ING3 mRNA expression but rare mutation found, suggests that a transcriptional mechanism, such as promoter methylation, may contribute to the HNSCC development (Gunduz et al., 2002).

Hepatocellular carcinoma

In the case of hepatocellular carcinoma (HCC), the analysis of ING3 mRNA expression revealed that in all the 49 tumor samples, ING3 was downregulated compared to normal livers. In addition, the expression of ING3 mRNA is reduced in 18 HCC cell lines compared to noncancerous cell lines. Moreover, in 64/112 samples of HCC, a downregulation of ING3 protein expression was found, while 24/112 samples had an upregulation of ING3 and 24/112 exhibited the same expression of ING3 protein. However, the overexpression of ING3 suppresses cell proliferation in Hep3B cell line, thus confirming that ING3 may be tumor suppressor gene (Lu et al., 2012). Another study showed that 16/20 patients with HCC exhibited a downregulation of ING3 protein and ING3 mRNA expression. In addition, in 4/6 hepatic cell lines, there is a downregulation of ING3 protein and ING3 mRNA expression (Yang et al., 2012).

Lung cancer

In two lung cancer cell lines, a downregulation of ING3v1 and v3 transcripts has been detected (Walzak et al., 2008).

Ovarian cancer

ING3v1 and ING3v3 showed a weak decrease of mRNA expression, in 1/1 ovarian cancer cell line GI-102 (Walzak et al., 2008).

Pancreatic cancer

In GI-103 pancreatic cell line, mRNA expression of ING3v3 transcript is downregulated but, surprisingly, ING3v1 is upregulated (Walzak et al., 2008).

Prostate cancer

In PC3 prostate cancer cell line, mRNA expression levels of ING3v1 and v3 are decreased (Walzak et al., 2008).

References

Awe JP, Byrne JA. Identifying candidate oocyte reprogramming factors using cross-species global transcriptional analysis. Cell Reprogram. 2013 Apr;15(2):126-33

Bienz M. The PHD finger, a nuclear protein-interaction domain. Trends Biochem Sci. 2006 Jan;31(1):35-40

Borkosky SS, Gunduz M, Beder L, Tsujigiwa H, Tamamura R, Gunduz E, Katase N, Rodriguez AP, Sasaki A, Nagai N, Nagatsuka H. Allelic loss of the ING gene family loci is a frequent event in ameloblastoma. Oncol Res. 2010;18(10):509-18

Doyon Y, Selleck W, Lane WS, Tan S, Côté J. Structural and functional conservation of the NuA4 histone acetyltransferase complex from yeast to humans. Mol Cell Biol. 2004 Mar;24(5):1884-96

Garkavtsev I, Kazarov A, Gudkov A, Riabowol K. Suppression of the novel growth inhibitor p33ING1

promotes neoplastic transformation. Nat Genet. 1996 Dec;14(4):415-20

Gou WF, Sun HZ, Zhao S, Niu ZF, Mao XY, Takano Y, Zheng HC. Downregulated inhibitor of growth 3 (ING3) expression during colorectal carcinogenesis. Indian J Med Res. 2014 Apr;139(4):561-7

Gunduz M, Ouchida M, Fukushima K, Ito S, Jitsumori Y, Nakashima T, Nagai N, Nishizaki K, Shimizu K. Allelic loss and reduced expression of the ING3, a candidate tumor suppressor gene at 7q31, in human head and neck cancers. Oncogene. 2002 Jun 27;21(28):4462-70

He GH, Helbing CC, Wagner MJ, Sensen CW, Riabowol K. Phylogenetic analysis of the ING family of PHD finger proteins. Mol Biol Evol. 2005 Jan;22(1):104-16

Lu M, Chen F, Wang Q, Wang K, Pan Q, Zhang X. Downregulation of inhibitor of growth 3 is correlated with tumorigenesis and progression of hepatocellular carcinoma. Oncol Lett. 2012 Jul;4(1):47-52

Mellor J. It takes a PHD to read the histone code. Cell. 2006 Jul 14;126(1):22-4

Nagashima M, Shiseki M, Pedeux RM, Okamura S, Kitahama-Shiseki M, Miura K, Yokota J, Harris CC. A novel PHD-finger motif protein, p47ING3, modulates p53-mediated transcription, cell cycle control, and apoptosis. Oncogene. 2003 Jan 23;22(3):343-50

Suzuki S, Nozawa Y, Tsukamoto S, Kaneko T, Imai H, Minami N. ING3 is essential for asymmetric cell division during mouse oocyte maturation. PLoS One. 2013;8(9):e74749

Walzak AA, Veldhoen N, Feng X, Riabowol K, Helbing CC. Expression profiles of mRNA transcript variants encoding the human inhibitor of growth tumor suppressor gene family in normal and neoplastic tissues. Exp Cell Res. 2008 Jan 15;314(2):273-85

Wang Y, Dai DL, Martinka M, Li G. Prognostic significance of nuclear ING3 expression in human cutaneous melanoma. Clin Cancer Res. 2007 Jul 15;13(14):4111-6

Wang Y, Li G. ING3 promotes UV-induced apoptosis via Fas/caspase-8 pathway in melanoma cells. J Biol Chem. 2006 Apr 28;281(17):11887-93

Yang HY, Liu HL, Tian LT, Song RP, Song X, Yin DL, Liang YJ, Qu LD, Jiang HC, Liu JR, Liu LX. Expression and prognostic value of ING3 in human primary hepatocellular carcinoma. Exp Biol Med (Maywood). 2012 Apr;237(4):352-61

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